

## EDITORIAL COMMENT

# The Return of Cardiac Time Intervals

## The Phoenix Is Rising\*

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Nothing retains the shape of what it was, and Nature, always making old things new...Reborn in ageless likeness through the years. It is the bird Assyrians call the Phoenix . . . Of bark and spices, myrrh and cinnamon, and dies incense lifts his soul away. Then from his breast—or so the legend runs, a little Phoenix rises over him.

—From *Metamorphoses* by Ovid (43 BC to AD 18) (1)

The precision of normal cardiac mechanics, even to millisecond intervals, is nothing short of being astonishing. A good example of this is the coordinated sequence of left ventricular (LV) isovolumic relaxation, mitral valve opening, diastolic filling, isovolumic contraction, aortic valve opening, and LV ejection. Because myocardial relaxation and contraction are orchestrated by intracellular recycling of calcium ions, the timing of these cardiac events is related in fact to the health of myocardial cells. Clinicians are familiar with the diagnostic and prognostic implications of some of the cardiac intervals, which are audible at the bedside. They usually result from myocardial or valvular events, which are

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affected by function, hemodynamics, and electrical activity of the heart. Correctly auscultating an S4 or S3 gallop sound enables clinicians to diagnose abnormal myocardial relaxation, compliance, or both with elevated filling pressures. Atrial septal defect is suspected by fixed splitting of the second heart sound along with pulmonary outflow systolic murmur, bicuspid aortic valve is differentiated from mitral valve prolapse by the timing of a systolic click, respiratory variation of pulmonary ejection click differentiates it from the aortic ejection click, and the severity of mitral stenosis is assessed by the second heart sound to opening snap interval. Cardiac time intervals caused by motion of the myocardium are not audible but now can be recorded by a relatively new noninvasive technology, and they provide valuable mechanistic and diagnostic insight into systolic and diastolic function of the heart. In this issue of the *Journal*, a new cardiac time interval measured by tissue Doppler imaging

(TDI) is reported by Rivas-Goetz et al. (2) that is quite clever in its concept and clinical application.

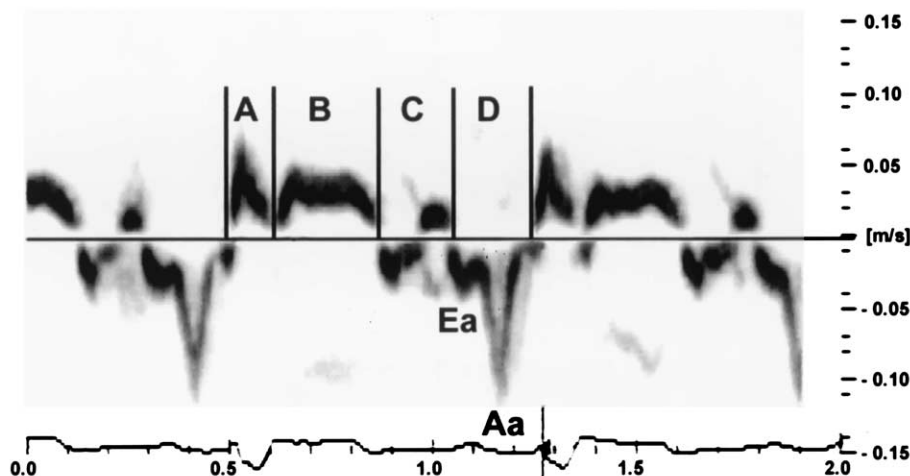
## CARDIAC TIME INTERVALS AS A MEASURE OF CARDIAC FUNCTION

More than 100 years ago, Marey, Garrod, and others were able to record the arterial pulse and systole (3). Those measurements were applied for the analysis of cardiac performance. Since then, various cardiac time intervals were measured noninvasively using sphygmography, phonocardiography, carotid pulse recording, apexcardiography, and echocardiography. More recently, TDI improved our ability to measure cardiac time intervals, including those generated by the movement of myocardial tissue. In the 1960s, the duration of isovolumetric contraction (IVCT) and pre-ejection period (PEP) were studied extensively as a measure of cardiac systolic function, and LV ejection time (LVET) was used as a measure of LV stroke volume. Although myocardial dysfunction prolongs PEP and shortens LVET, these intervals are also influenced by many hemodynamic and electrical variables. Weissler et al. (4) derived an index (PEP/LVET) called “systolic time interval,” which was less heart rate dependent as a measure of LV systolic function. However, the variability of this index as a measure of LV systolic dysfunction was significant and a lengthening of the systolic time interval was found to occur after LV systolic function deteriorated (5). Because isovolumic relaxation time (IVRT) is also affected by LV function, Mancini et al. (6) incorporated IVRT into an index called the “isovolumic index” derived as (IVCT + IVRT)/LVET. The sum of IVCT and IVRT was measured by subtracting the LVET from the peak of the R wave on the electrocardiogram to the onset of mitral valve opening. The isovolumic index was considered more sensitive for cardiac dysfunction than the systolic time interval because it contains IVRT as well as IVCT. However, the interval from the R wave peak to the onset of mitral valve opening contains an interval of electromechanical delay, which can be pronounced in patients with left bundle branch block. With the advent of Doppler echocardiography, it has become easier to determine cardiac time intervals more reliably. Tei et al. (7) proposed a “myocardial performance index” (or “Tei index”) that is independent of the electromechanical delay, (IVCT + IVRT)/LVET, using Doppler echocardiography to identify the exact onset of isovolumic contraction. The Tei index has been found to have prognostic value for various cardiac conditions (8,9).

Doppler recording of time intervals from mitral inflow and pulmonary vein velocities has allowed the reliable and practical noninvasive assessment of diastolic function or filling pattern. The deceleration time (DT) of early diastolic mitral inflow velocity (E) has been well correlated with pulmonary capillary wedge pressure (PCWP) (10), especially in subjects with decreased LV ejection fraction and

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**Figure 1.** Tissue Doppler recording of velocities from the mitral annulus demonstrating its ability to determine the timing of various cardiac events: (A) pre-ejection period or isovolumic contraction time; (B) left ventricular ejection time; (C) time from closure of the aortic valve to opening of the mitral valve; (D) diastolic filling period. Aa = mitral annulus velocity with atrial contraction; Ea = early diastolic velocity of the mitral annulus.

adds an incremental prognostic value to LV ejection fraction in patients with heart failure, cardiac amyloidosis, or acute myocardial infarction (11–13). Other time intervals measured by Doppler echocardiography, such as the duration of mitral atrial flow, the duration of pulmonary vein atrial flow reversal, and DT of diastolic pulmonary vein forward flow velocity, have been identified as intervals that can estimate diastolic filling pressures reliably enough to be used clinically (14).

## TISSUE DOPPLER IMAGING AND CARDIAC TIME INTERVALS

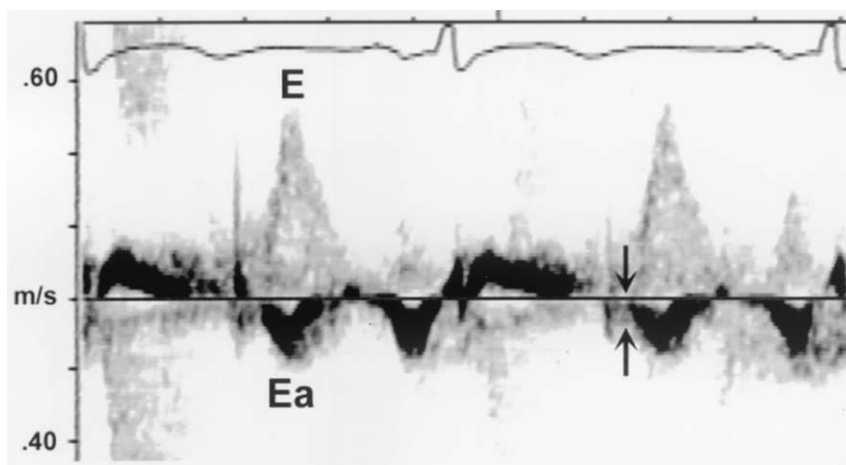
Recently, Doppler echocardiography has been modified to record velocities of myocardial tissue, which are lower in absolute value and higher in amplitude than those of the blood flow. The timing of myocardial events can be recorded exquisitely by using TDI with low-velocity and low-filter settings (Fig. 1). The accurate velocity recordings of mitral annulus, endocardium, and epicardium by TDI have been validated for determining cardiac filling pressures, intracavitary pressure gradient, and myocardial velocity gradient and for differentiating pericardial disease from myocardial disease responsible for heart failure (15–19). Another promising clinical area from measuring time intervals with TDI is to help identify patients who might benefit from cardiac resynchronization therapy because TDI can assess the degree of LV mechanical dyssynergy by precisely determining the time intervals between peak systolic contractions of different areas of the LV wall (20).

## MITRAL ANNULUS MOTION . . . NONINVASIVE TAU?

Mitral annulus motion was first recorded by digital M mode echocardiography and was found to be useful in assessing LV systolic and diastolic functions. An important observation made with tissue velocity recorded by TDI was that the early diastolic velocity of the mitral annulus is relatively

independent of preload and closely related to the rate of myocardial relaxation as determined by tau (15). It was discovered, however, that the extent of mitral annulus motion depends on the transmitral gradient in subjects with well-preserved myocardial relaxation. Further investigations demonstrated the relative preload independence of the early diastolic velocity (Ea) of mitral annulus in patients with impaired relaxation and Ea was shown to be less affected by a change in transmitral gradient. This relatively flat response of Ea to preload compared with a progressive increase in E with higher LA pressure gave rise to the ratio, E/Ea, as a reliable means to estimate LV filling pressure. If E/Ea is >15, pulmonary capillary wedge pressure is usually 20 mm Hg or higher (16,17).

The different responses of E and Ea velocities to an increase in preload illustrate the different mechanisms generating E and Ea velocities: When LV myocardial relaxation is normal, E begins with LV diastolic suction induced by rapid relaxation resulting in a simultaneous onset of E and Ea. However, if myocardial relaxation is impaired, early diastolic filling is initiated by LA pressure at the time of mitral valve opening and Ea velocity starts later as a result of delayed myocardial relaxation. Rivas-Gotz and his colleagues (2) demonstrate convincingly that the timing of E and Ea is regulated by LV filling pressure and myocardial relaxation, respectively. The time interval between the onset of mitral inflow E and of Ea ( $T_{Ea} - E$ ) was found to correlate well with tau and LV minimal pressure measured in experimental animal model, in which the circumflex coronary artery was constricted to alter the tau and the inferior vena cava was occluded to manipulate preload. Using the previously reported equation,  $PCWP = LV_{es} \times e^{-IVRT/\tau}$  and  $T_{Ea} - E$  in place of tau, the authors found a good correlation between the catheter PCWP and Doppler-derived PCWP ( $= LV_{es} \times e^{-IVRT/T_{Ea} - E}$ ) in human subjects. Because the equation was difficult to use clinically, the relationship between  $T_{Ea} - E$  and PCWP was simplified



**Figure 2.** Pulsed wave Doppler recording from the apex of both mitral inflow (E) and mitral annulus velocity (Ea) with a sample volume between the septal mitral annulus and anterior mitral leaflet. The simultaneous onset of both E and Ea (arrows) are well recorded in this subject who has normal diastolic function. Note that the intensity of the Ea recording is greater than that of E because their amplitudes are different.

fied. A ratio of  $IVRT/T_{Ea - E} < 2$  had a sensitivity of 80% and a specificity of 90% in identifying patients with PCWP  $> 15$  mm Hg.

## COMMENTS

Whether this novel index will become a preferred noninvasive means to assess LV diastolic function and filling pressures depends on its practicality and incremental value to other more easily available measures such as mitral DT, Ea, and the E/Ea ratio. Measuring time intervals is more difficult and variable than measuring peak velocities. To use  $IVRT/T_{Ea - E} < 2$  requires three separately measured time intervals. Moreover, Ea needs to be averaged from four separate sites of the mitral annulus. It is not certain how a slight change in cycle length affects these time intervals. Because  $T_{Ea - E}$  from a single mitral annulus site was reasonably sensitive for predicting increased filling pressure, it will be ideal if these time intervals can be recorded simultaneously. The simultaneous recording of the onset of both mitral E and Ea may be possible using the regular pulsed-wave Doppler echocardiography with a sample volume placed between the septal (or lateral) mitral annulus and the mitral leaflet (Fig. 2). If this is feasible in most patients, the suggested ratio will be more practical in routine assessment of diastolic function noninvasively. In patients with clinically obvious systolic or diastolic dysfunction, this new index may not add a great deal to what is currently available and more easily obtainable Doppler parameters for estimation of filling pressures. Because both peak  $E_a$  velocity and  $T_{Ea - E}$  are related to tau, it would have been nice to see correlation between two measures.

The validation of a delay in Ea, as compared with mitral inflow E velocity, when myocardial relaxation is impaired contributes importantly to understanding the mechanics of diastolic filling. A few months ago in this *Journal*, Hasegawa and colleagues (21) reported in dogs with pacing-induced heart failure that peak mitral inflow E velocity occurred

coincidentally with the termination of the early diastolic transmitral gradient whereas Ea was progressively delayed by  $37 \pm 12$  ms after equilibration of the transmitral pressure gradient. The maintenance of normal cardiac time intervals is intimately related to normal cardiac physiology, mechanics, and hemodynamics. When these are disturbed, cardiac time intervals are shortened or delayed. Our ability to measure these millisecond intervals has enhanced our understanding of the well-orchestrated timing of cardiac events and has improved the diagnostic assessment of cardiac function. As noninvasive imaging and Doppler technology have improved, measuring cardiac time intervals has become easier and more precise. Whether the novel index introduced by Rivas-Gotz and colleagues (2) will become a practical way for estimating pulmonary wedge pressure and under what circumstances it will provide incremental value to existing Doppler measures will require further experience and validation. Nevertheless, it is clearly evident that just like the fabulous Phoenix, cardiac time intervals are rising again with a new vigor and greater precision.

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